PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors Predicting Self-Reported Medication Low Adherence in a Large Sample of Adults in the US General Population: A Cross-sectional Study
AUTHORS	Feehan, Michael; Morrison, Margaux; Tak, Casey; Morisky, Donald; DeAngelis, M; Munger, Mark

VERSION 1 - REVIEW

REVIEWER	Elizabeth Unni Roseman University of Health Sciences College of Pharmacy, United States
REVIEW RETURNED	12-Oct-2016

GENERAL COMMENTS	General comments: The study has the advantage of surveying a national sample and a large sample size. However, the variables measured are also the same that can be derived from a retrospective database. Examples are age, visits to the emergency room, care delivered through a hospital or urgent care, visit to primary care doctor, number of providers, number of comorbid conditions, insurance status, etc. All these variables have been studied in the past. The WHO report "Adherence to long-term therapies: Evidence for action" has most of these variables already explained in "The five dimensions of adherence". See the excerpt below from the WHO report. "Some factors reported to have a significant effect on adherence are: poor socioeconomic status, poverty, illiteracy, low level of education, unemployment, lack of effective social support networks, unstable living conditions, long distance from treatment centre, high cost of transport, high cost of medication, changing environmental situations, culture and lay beliefs about illness and treatment, and family dysfunction. Various sociodemographic and economic variables are discussed in the course of this report" Additionally, the current adherence literature is moving away from adherence in general to adherence to specific medicine for each individual. A person adherent with one medicine can be non-adherent with another medicine. So, when asked in general, there can be a tendency to report as adherent when adherent with one medicine and non-adherent with another medicine. This can also cause underestimation of non-adherence. In summary, though the study has been conducted well and reported well, I am not entirely convinced that it is adding more to the adherence literature. If the investigators have collected any other patient reported outcomes such as treatment burden, communication with providers, self-efficacy, beliefs in medicines and illnesses, etc. either reporting it or making mention of it as future

	publication can add value. Specific comments: The primary outcome variable for the study is medication adherence and it was measured using the MMAS-8scale. However, though MMAS -8 is a well validated scale, it is not a comprehensive scale and miss several important reasons for non-adherence, manly cost. Thus, the 42% non-adherence reported by the study can be an underestimated value. Instead of reporting the MMAS-8 scale as in the literature, may be just reporting the percentage of respondents who answered “yes” to Questions 1 and 2 in the MMAS-8 scale may give a better picture. When looking at age, comparing those above 65 to those below 65 is not adequate. The 18 to 64 years cohort may have distinct adherence patterns based on their age. For example, 18 to 25 (mostly single and in college) can be different from 26 to 45 (married with young family) compared to 46 to 64. A comparison between all these ages keeping 18to 25 as reference can be a better predicting model. Similarly, comparing insured to non-insured is not anything new. However, if you have collected data on “out of pocket expenses every month”, then comparing high out of pocket expenses to low out of pocket expenses among the insured can be interesting.

REVIEWER	Shoshana Kahana NIH
REVIEW RETURNED	15-Nov-2016

GENERAL COMMENTS	Thank you for this opportunity to review this thoughtful and interesting article. The manuscript could be significantly strengthened if the following 3 issues could be addressed: 1)The innovation of the current findings. There are multiple recent findings suggesting low rates of medication adherence in the US (in fact, one white paper from 2013 Express Scripts actually calculates the estimated direct and indirect costs of nonadherence across the US). So it would be helpful for this reviewer to have the authors make a sharper case for the innovative and unique purpose and findings in this paper. 2) There is no conceptual framework that seems to explain the particular correlates of low adherence that the authors examined. In addition, there were other correlates that one might have expected to see, including illness type, illness severity, pill regimen, length of being sick etc. 3) Were there issues of multicollinearity in the multivariate model and if so how was this handled?

REVIEWER	Angela Lupattelli School of Pharmacy, University of Oslo, Norway
REVIEW RETURNED	25-Dec-2016

GENERAL COMMENTS	Thank you for giving me the opportunity to review this manuscript.

	The authors conducted a cross-sectional study to examine the extent of and factors related to low medication adherence in the US general population. In general, this is an important topic, however the study has several drawbacks that should be addressed by the authors. Introduction: The Introduction is well written and provides a clear description of medication adherence. The authors list a set of patient characteristics associated with low adherence (lines 41-44, page 1), however it would be interesting for the reader to know the magnitude of these associations, at least for the strongest predictor(s). Research on patients' beliefs and attitudes towards medication, and how these factors related to medication adherence has been conducted; any reason why these specific characteristics were not covered in the Introduction? The importance of patients' beliefs on medicines in relation to medication adherence could be mentioned here. The authors should highlight what this study adds to the current literature in terms of novelty. Methods: this section should be amended with more details about the sampling method of the 10,006 adults, and about the eligibility screening procedure. It should also be clarified what type of prescriptions (one of the eligibility criteria: 3 prescriptions or more in the last 12 months) the study is dealing with (long-term or chronic medications, antibiotics?) I could not find this information among the baseline characteristics shown in table 1. I feel this is important information in order to better understand the baseline characteristics of the sample. Please clarify what it is meant by "nonsensical data"; it seems that 8% of the respondents provided nonsensical data and were excluded. This seems to be a pretty high proportion. Measures: please specify whether the MMAS was administered in English and Spanish, or only in English. It should be explained whether the MMAS was medication-specific or disease-specific; if a "general" format of the MMAS was used, then it is challenging to appraise what type of medication adherence the study is dealing with. It is should be at least discussed/presented if the study is dealing with adherence for chronic medication or adherence to short-term treatments. The statistical section is not sufficiently described. Candidate variables for the multivariate model were selected based on a p-value < 0.05 from the univariate model results. However, with this approach there is the possibility to miss out important predictors; generally a p-value of 0.20 is recommended for the selection of candidate variables for the multivariate model (see Hosmer). The Methods section does not give any information about how the most parsimonious predictor model was achieved (i.e. how removal of explanatory variables was conducted and tested), testing of possible interactions, model fit. The authors should also describe how missing data were handled in the study. The authors performed an overall analysis including patients with different disease/pharmacotherapies, and at the same time patients from different states in the USA. A clustering of data (by pharmacotherapy/disease, or state) is therefore possible. Sensitivity

	analyses accounting for this potential factor should be conducted to test the robustness of the results. Results: The readership would probably be interested in knowing the medications/pharmacotherapies the study is dealing with, in order to better appraise the estimates of low medication adherence. It would be nice to see the extent of low medication adherence by disease type/pharmacotherapy, at least for the most common ones. Although the authors aimed to explore low medication adherence across conditions, it should be clarified somewhere whether the study is solely dealing with chronic pharmacotherapies, or also with short-term pharmacotherapies. By reading Table 2, it appears that health status and health insurance, for instance, were not retained in the final multivariate model. However, the reader needs to know the procedure applied for the selection of variables retained in the final model. The Discussion is lacking reflections about the lack of clinical outcomes in this study. It is important to estimate the prevalence and correlated of low medication adherence, but it would be even more important to know the consequences (if any) of low medication adherence on patients' health. Comparison with previous research may be limited by how medication adherence was assessed and presented in the current study; is it reasonable to compare low medication adherence for any medication to low adherence to antihypertensive drugs, for instance?

REVIEWER	Sagnik Bhattacharyya King's College London, UK
REVIEW RETURNED	11-Jan-2017

GENERAL COMMENTS	This is an interesting and important study investigating predictors of adherence in a general population sample. Adherence was measured using a self-reported survey. I have the following comments/ suggestions on the manuscript in its present form. The authors should elaborate more on the regression analyses employed- eg was it ordinal logistic regression (or did they create two categories low adherence vs rest and use binary logistic regression instead)? Age has been used as a categorical variable with a cut-off of 65 years. Is that because that is how the data is available? Perhaps the authors could consider using age as a continuous variable or at least split into more levels, if such information is available or at least discuss this as a limitation. One wonders whether the effect of age on adherence is similar over the 18-65 years range or different at the lower end of that range. Another important factor that might have a bearing on adherence is the nature of the condition that the person is receiving treatment for. Do the authors have access to this information? Perhaps in that case it may be useful to consider a 'disease type' predictor with a number of meaningful categories to summarize the types of conditions being treated.

VERSION 1 – AUTHOR RESPONSE

Author's Response to Decision Letter for (bmjopen-2016-014435)

Factors Predicting Self-Reported Medication Low Adherence in a Large Sample of Adults in the US General Population

We thank the reviewers for their considered and constructive comments and have taken the opportunity to completely revise the analyses and model in by using multiple age categories as recommended by two of the reviewers, to accommodate finer granularity in the under 65 age group.

RESPONSE TO REVIEWER 1: The reviewer is correct in that some of the data are similar to those available from retrospective databases (e.g., claims data, pharmacy refill data), but we also noted the need for self-report explication beyond database abstraction in the introduction. We are very familiar with these kind of database analyses and cited one such paper using refill data on asthma in the original submission (Feehan et al., Clinical Pharmacy and Therapeutics. 2015:Aug 20.) Since then we have published a second paper using glaucoma medication refill data (which has a very different mode of administration) and included that reference in the revision (Feehan et al., Journal of Clinical Medicine. 2016: Sep; 5(9): 79.) As noted in those papers is the lack of availability of self-reported adherence metrics and any psychosocial factors available through self-report only such as barriers to access (as used in the present study). By default, use of retrospective databases implies that the respondents had access to whatever services provided those database reports.

The reviewer notes that some adherence literature is condition and/or medication specific. We certainly concur – that is reflected, for example, in the two papers from our group cited above focusing on asthma and glaucoma. The reviewer's observation that "…there can be a tendency to report as adherent when adherent with one medicine and non-adherent with another medicine. This can also cause underestimation of non-adherence" is quite valid and the discussion has been amended to include this in the limitations section.

The reviewer cites from the well-known 2003 WHO report "adherence to long-term therapies" which we cited in our introduction. We have used this opportunity to correct the reference in the manuscript (adding Sabate, the first author). We have also expanded the introduction to explicitly note the lack of epidemiological data on self-reported adherence across sub-groups of the US population. The rationale for the present study and its importance.

The reviewer asked for additional self-report data on factor such as "treatment burden, communication with providers, self-efficacy, beliefs in medicines and illnesses". While we certainly agree that more data is always helpful, unfortunately these data were not collected in our study given restrictions in survey length.

The reviewer asks for alternate analyses using only sub items from the Morisky scale. This is not permissible under the license agreement for use of the scale, and moreover would likely be unpublishable as other reviewers would challenge the lack of psychometric data on the use of only select single items from the validated full scale.

The reviewer also notes that the scale is not totally comprehensive, an issue which we can not resolve – we used the best known self-report measure in the literature that is recommended by several professional healthcare organizations and has been (as the reviewer notes and we cite in the paper) comprehensively validated. The reviewer suggests that the scale does not include cost which is true. However, we addressed the access barrier of meeting the cost of medications as one of the key barriers presumptively leading to lower adherence and it remained a key predictor in our multivariate analyses. The reviewer also asked for further cost data - "out of pocket expenses every month", which are not available in our survey, and as noted we addressed perceive difficulty in meeting costs as a key driver in our model.

Per the reviewer's recommendation we have broken out the age classifications into ages 18-25, 26-45, 46-64 and 65+. The distributions of these breaks is now shown in Table 1, and described in the results section. Table 2 shows the univariate associations of these age groups, and their inclusion in the revised multivariate model (referencing the youngest age as the comparator as per the other reviewer's recommendation), and is described in the results section and referenced in the discussion.

RESPONSE TO REVIEWER 2: We have added a paragraph to highlight the need for self-report epidemiology in the US with a large sample. We had conducted a pubmed literature search and recent large-scale epidemiological survey data on US adherence are not readily evident. It would have been helpful if the reviewer had provided a source for the multiple recent findings they mention, outside of database analyses. Again, there is a paucity of national-level US self-report data and self-reported correlational data on factors contributing to that adherence. The reference to an unpublished white paper from a commercial company (Express Scripts) is not particularly helpful, as we cannot see that particular citation. Was this survey data from the general population – or calculations from their dispensing database? We are aware of a published adherence article from Express Scripts (Iyengar et al, Am J Manag Care. 2013;19(10):798-804) which was not cited as it focused on a particular issue – home delivery of medications and associated higher adherence (again, utilizing claims data not patient self-report).

While we would have liked to include a deeper exploration of factors recommended by the reviewer such as illness type, illness severity, pill regimen, length of being sick etc. – these data are not available. Other measures in the survey not at all related to this adherence study on adherence (pharmacy services evaluation) are being published elsewhere which limited the survey length - this has been noted in the methods section.

No issues regarding multicollinearity in the multivariate model were observed. The statistical analysis section now includes a reference to that effect.

RESPONSE TO REVIEWER 3: The magnitude of the predictors in the Raeburn article are challenging to cite as they encompass three medication classes, but we have included the highest AOR.

While we would have liked to include a deeper exploration of factors recommended by the reviewer such as patients' beliefs and attitudes towards medication – these data are not available. Other measures in the survey not at all related to this adherence study on adherence (pharmacy services evaluation) are being published elsewhere which limited the survey length - this has been noted in the methods section.

We have also expanded the introduction to explicitly note the lack of epidemiological data on self-reported adherence across sub-groups of the US population. The rationale for the present study and its importance.

We are very familiar with Hosmer and Lemeshow's 'recommendation' of .20 for inclusion of candidate variables, and have indeed used that criterion in other published studies (with lower N's). However, in this study with a large sample size and the conduct of many independent univariate tests of association we used a more parsimonious and conservative approach of inclusion (.05). This helps avoid the inclusion of spurious associations which can lead to multicollinearity issues (in several other studies we have published citing multiple univariate tests we also apply a Bonferroni correction to adjust for the enhanced likelihood of spurious associations). This conservative approach has been noted in the statistical methods section.

In terms of other specific comments: (a) respondents were screened to have filled prescriptions to ensure they were users of pharmacy services, no further data on type of proscriptions are available – now noted in the methods); (b) the survey was administered in English – now noted in the methods, and included as a limitation in the discussion; (c) the MMAS-8 was used to assess for low-adherence in general, not for specific conditions or medications – now noted in

the methods; (d) since those with nonsensical data were not included in analyses there were no missing data in the final analyses; (e) the final model fit is shown in the results with the C-statistic (0.7) and the reference for its used cited in the references (Hosmer and Lemeshow); (f) the methods have been updated to include more information on the sampling procedure; (g) 'nonsensical data' has been fleshed out; (h) interaction terms were not included in the model; (i) as seen in table 2, there was no significant associations between geographic location in associations with adherence, doing some kind of multilevel hierarchical analysis is simply gilding the lilly unlikely to yield manifestly different results and is beyond the scope of this paper; (j) no information on the medications people were taking are available – this is now noted in the methods; (k) we agree it would be good to know more about the consequences of low adherence, but other health outcomes data are not available in this dataset – we will be doing further research on this in the future.

RESPONSE TO REVIEWER 4: The analysis utilized binary logistic regression and this has been noted in the statistical analysis section.

Per this reviewer and another's recommendation, we have broken out the age classifications into ages 18-25, 26-45, 46-64 and 65+. The distributions of these breaks is now shown in Table 1, and described in the results section. Table 2 shows the univariate associations of these age groups, and their inclusion in the multivariate model (referencing the youngest age as the comparator as per the other reviewers recommendation), and is described in the results section and referenced in the discussion.

A disease comorbidity score is included in the analysis and its association with low adherence was non-significant. No specific medications were obtained, and no information is available linking adherence reports to disease states as adherence was asked at the overall level –this is now noted in the methods.

VERSION 2 – REVIEW

REVIEWER	Angela Lupattelli School of Pharmacy, University of Oslo, Norway
REVIEW RETURNED	20-Feb-2017

GENERAL COMMENTS	The authors have satisfactorily addressed my concerns.

REVIEWER	Dr Sagnik Bhattacharyya King's College London, UK
REVIEW RETURNED	26-Apr-2017

GENERAL COMMENTS	The authors have addressed the issues raised in review.